Procter&Gamble
PHARMACEUTICALS

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August 27, 1999

Documents Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane.
Rm 1061
Rockville, MD 20852

Re: Docket Number 99D-0529

Dear Sir or Madam:

Procter & Gamble Pharmaceuticals has reviewed the Draft Guidance for Industry, Changes to an Approved NDA or ANDA . In general, this guidance around the proposed rule for revisions to 21 CFR 314.70 is well compiled and detailed. To the extent that it contains many more specifics about FDA's expectations about changes to an approved NDA or ANDA it is useful. In addition there are some instances where it provides some relaxation of the current requirements. However, it contains several requirements which are more stringent and burdensome than current practice, thus decreasing the regulatory relief and increasing regulatory burden. We believe that the intent of the FDA Modernization Act was to identify a small number of major manufacturing changes that require prior approval but that most changes would require a less burdensome means of reporting than has been required in the past. However, it appears that FDA has used the change in the law as an opportunity to codify their current thinking about the reporting requirements for reporting changes, with some minor changes in the specifics, rather than rethinking its policy on changes. Finally, although the guidance introduces the concept of comparability protocols, it lacks any information on comparability protocols, a key provision added on as 314.70(e).

Although the proposed rule and draft guidance are being worked in parallel, it may have been better to finalize the regulations before issuing the guidance, since the guidance would have to be revised in accordance with the revisions to the proposed rule. Specific comments are attached with reference to line number. Some of these comments also apply to the proposed rule in re-classification of requirements, however specifics on the proposed rule will be covered by another letter.

If there are any questions or if I can be of further assistance, feel free to call on me.

Sincerely,

Harry L. Welles

Harry L. Welles, Ph.D.
Principal Scientist
Regulatory Affairs

99D-0529

C 2H

2000 HOLIDAY SCHEDULE

January 3	Monday	New Year's Day Holiday
January 17	Monday	Martin Luther King Jr's. Birthday Holiday
February 21	Monday	President's Day Holiday
April 21	Friday	Good Friday Holiday
May 29	Monday	Memorial Day Holiday
July 4	Tuesday	Independence Day Holiday
September 4	Monday	Labor Day Holiday
November 23	Thursday	Thanksgiving Day Holiday
November 24	Friday	Day After Thanksgiving Holiday
December 22	Friday	Christmas Eve Holiday (Observed)
December 25	Monday	Christmas Day Holiday
December 29	Friday	New Year's Eve Holiday (Observed)

Two Personal Holidays

New Year's Day Holiday will be celebrated on Monday, January 1, 2001

C. W. Thompson
NA Employee Relations

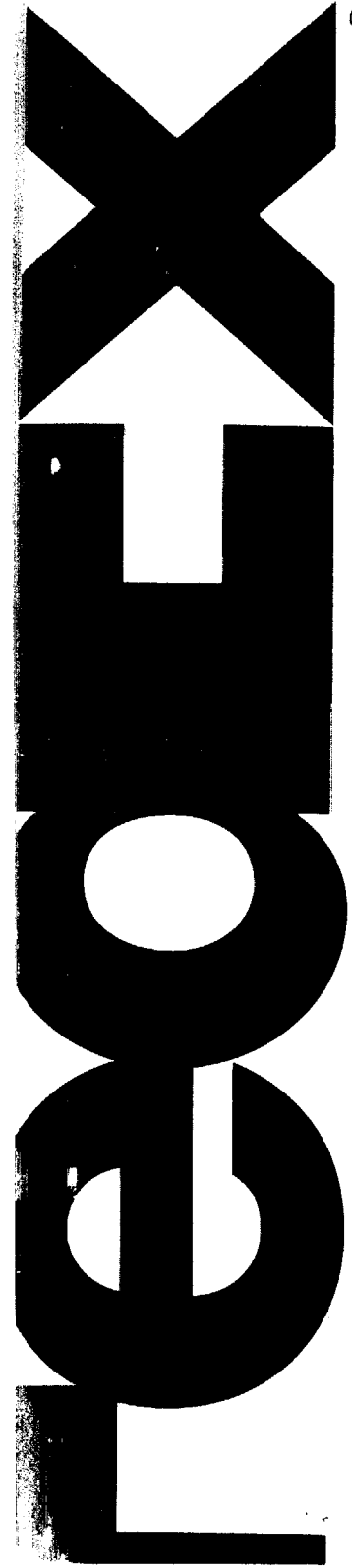
Please note that for 2000, the Christmas Eve Holiday will be observed on Friday, December 22 and the New Year's Eve Holiday will be observed on Friday, December 29, 2000.

Posted 8/23/99 - 9/3/99

Lines	Change
88-89	Change "list all" to "provide a brief summary of major". In an active submission, complete listing of all minor changes in the cover letter to the Annual Report is not likely to be useful. Also there is no regulatory requirement that an Annual Report have a cover letter.
97-98 745-746	Delete the requirement to provide 12 copies of the final printed labeling with a CBE labeling supplement. Although the specified changes may be submitted in a CBE, at times they may not be implemented until some time after the submission. To print final labeling specifically for the CBE is unnecessarily expensive and complicates the normal labeling printing process. An alternative would be to submit a typed copy of the labeling, and submit the final printed labeling in the Annual Report.
212-213	The term "type of operation" needs to be defined. For example, if a drug substance manufacturer chooses to manufacture a drug substance with a new route but using the same equipment, is it considered a new type of operation and does this need an inspection? This needs to be clarified. The prior approval supplement is also considered too stringent and unnecessary for the cases mentioned. It is contradictory to other guidances being developed by the FDA, i.e., BACPAC-I.
222-238	This paragraph is confusing and it would be helpful to simplify it. It appears that it is trying to convey the thought that the significance of certain changes is independent of the type of product in question and provide examples. The significance of other changes is dependent on the type of product. Presentation along these lines would be helpful.
239-243	Following this paragraph, a statement on secondary packaging facilities is necessary. Also, the FDA inspection requirements stated in paragraph 211-221 should be exempt for secondary packaging facilities.
251-252	The concern about moving to a site where an operation has been discontinued and is now being restarted may or may not be a valid one depending on the length of time the operation has been discontinued. Short interruptions in certain types of manufacturing are not uncommon and should not be of concern. We suggest that only discontinuation for more than two years should cause a site change to be considered a major change.
256-261	The changes described in point 3 are really combination changes and should be considered as such. There should be a general statement that combination changes require the most stringent reporting requirements of each of the individual changes, then point 3 will not be necessary.

Lines	Change
263-264	The formulation almost invariably controls the dose delivered to the patient. This section might be clearer if it is worded "of (1) drug products when the primary packaging components control the dose delivered to the patent, or the formulation modifies the rate or extent of availability of the drug ..."
273	For clarity, insert after facility the words "not currently the subject of an approved application for this type of manufacturing" .
290	For clarity, insert the word "sterile" before "drug product".
294-300	Requiring a CBE with 30 day notification for a change in testing facilities is excessive if all of the conditions under point d. are met. If the methods are approved, all post-approval commitments are met, the facility has a satisfactory inspection history, and the facility is capable of performing the testing, there is very little likelihood of an adverse impact on the product. This change should be an Annual Report change.
303-304	Moving the manufacturing site for a final intermediate poses very little risk if the methods are capable and the specifications are met. This change should be an Annual Report change.
305-309	The requirements for moving the manufacturing site of drug substance manufacturing should not be based on who is the owner of the site. As long as appropriate change control is done, this should be an Annual Report item.
314	Delete "on the same (i.e., contiguous)". It is unnecessarily detailed to specify the location of the secondary packaging location on a site or campus.
316	Delete "on the same or". It is unnecessarily detailed to specify the location of the labeling location on a site or campus.
368-369	The requirements for embossing, debossing or engraving on a modified solid oral dosage form are too stringent. This needs to be re-classified as a Supplement-Changes Being Effected.
392-397	There appears to be no scientific basis for the choice of the 50% figure. Unless FDA has some data to support this number, changes discussed in this section should be validated and subject to the same types of change requirements as other dosage forms.
435, 442, 445 and 462	These changes should be re-classified under Supplement-Changes Being Effected. They are not likely to affect the quality of the product.
539	Add "or minor changes" at the end of the sentence.

Lines	Change
544-550	The situation provided here is highly unlikely and therefore, can be deleted
567-571	This section should read "Any change to comply with an official compendium." and the rest of the section should be deleted. Because the USP/NF is the legal standard for monographed products, there should be no qualifications in the guideline that require interpretation or put the applicant in the middle of a disagreement between FDA and USP. It is understood that the NDA or ANDA may have some additional requirements that are not listed in the USP, such as additional impurities specifications for a API, but this section does not appear to address this situation.
573-576	Delete everything after "procedure". The manufacturer should be responsible for determining the appropriateness of an alternate analytical method.
584-585	Delete this section. The regulations or existing guidelines do not require submission of specifications for reference standards, and should not. The 1987 drug substance guideline suggests that the reference standards should be described, which is common practice. However, it is not common practice to update this information after the initial submission. This section represents a new regulatory requirement that does not have a basis in the law or regulations and is not necessary to protect product quality.
661	The requirements for a change in size and/or shape of a container containing a different number of dose units, for a non-sterile solid dosage form are not provided. This change should be reported through an Annual Report.
778	The approval of a comparability protocol should be through a Supplement-Changes Being Effected-30 days since the change is not actually being implemented but includes a proposal or plan to address in the future. Therefore a significant wait should not be necessary.
794-799	Delete. The regulations or existing guidelines do not require submission of specifications for reference standards, and should not. The 1987 drug substance guideline suggests that the reference standards should be described, which is common practice. However, it is not common practice to update this information after the initial submission. This section represents a new regulatory requirement that does not have a basis in the law or regulations and is unnecessary.
799	Include variations to the size and shape of the dosage form as miscellaneous change requiring Annual Report notification providing that the change is validated.



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